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The significance of haematological parameters and CA 19-9 in assessing vascular invasion and inoperability in pancreatic cancer

Pankreas kanserinde vasküler invazyon ve inoperabilitenin değerlendirilmesinde hematolojik parametrelerin ve CA 19-9'un önemi

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ABSTRACT

Aim: In this study, by comparing resectable and unresectable patients over the laboratory data of patients with pancreatic cancer, the predictive usefulness of haematological parameters and CA19-9 in the evaluation of inoperability was explored.

Material and Method: The study included 147 individuals diagnosed with pancreatic cancer at Hitit Univesity Erol Olçok Training and Research Hospital between 2015 and 2021. Patients were divided into two groups: those who had surgery (group 1) and those who were unable to have surgery (group 2). The platelet/mean platelet volume ratio (P/MPV), platelet/platelet distribution volume ratio (P/PDW), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and C- reactive protein/lymphocyte ratios (CRP/L) were all calculated.

Result: When the patients' NLR, mass size, CRP/L, CRP, and CA-19.9 levels were compared between groups, a significant difference was observed. When the age, NLR, mass size, P/PDW, P/MPV, CRP (C reactive protein), CRP/L, platelet distribution volume (PDW), and CA 19-9 values of patients in Group 2 with superior mesenteric artery (SMA) and superior mesenteric vein (SMV) invasion (n:26) were compared to those in Group I, a statistical difference was detected.

Conclusion: In this study, NLR, CRP, CRP/L, CA 19-9 levels, and tumour mass were revealed to be significantly relevant in determining the chance of resectable surgery. In cases of unresectability or vascular invasion, we anticipate that these values can assist us prevent unnecessary laparotomies.

Keywords: Pancreatic cancer, vascular invasion, unresectability

ÖZ

Amaç: Bu çalışmada, pankreas kanserli hastaların laboratuvar verileri üzerinden rezeke edilebilen ve edilemeyen hastalar karşılaştırılarak, hematolojik parametrelerin ve CA19-9'un inoperabilitenin değerlendirilmesinde prediktif faydası araştırıldı.

Gereç ve Yöntem: Çalışmaya 2015-2021 yılları arasında Hitit Üniversitesi Erol Olçok Eğitim ve Araştırma Hastanesi'nde pankreas kanseri teşhisi konan 147 birey dahil edildi. Hastalar ameliyat olanlar (grup 1) ve ameliyat olamayanlar (grup 2) olmak üzere iki gruba ayrıldı. Trombosit/ortalama trombosit hacim oranı (P/MPV), trombosit/trombosit dağılım hacim oranı (P/PDW), nötrofil/lenfosit oranı (NLR), lenfosit/monosit oranı (LMR) ve C-reaktif protein/lenfosit (CRP/L) oranları hesaplandı.

Bulgular: Hastaların NLO, kitle boyutu, CRP/L, C reaktif protein (CRP) ve Ca-19.9 düzeyleri gruplar arasında karşılaştırıldığında anlamlı fark görüldü. Grup 2'de yer alan ve superior mezenterik arter (SMA), superior mesenteric ven (SMV) invazyonu olan hastalar (n:26) Grup I ile karşılaştırıldığında; yaş, NLR, kitle boyutu, P/PDW, P/MPV, CRP, CRP/L, trombosit dağılım hacim (PDW) ve Ca 19-9 değerleri arasında istatistiksel fark saptandı.

Sonuç: Bu çalışmada, NLR, CRP, CRP/L, CA 19-9 seviyeleri ve tümör kitlesinin, rezektabl cerrahi şansını belirlemede önemli ölçüde ilişkili olduğu ortaya çıktı. Rezektabl olmama veya vasküler invazyon durumlarında, bu değerlerin gereksiz laparotomileri önlememize yardımcı olabileceğini tahmin ediyoruz.

Anahtar Kelimeler: Pankreas kanseri, vasküler invazyon, rezektabl olmama

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INTRODUCTION

Pancreatic cancer has a high propensity for local invasion, hematogenous spread, has a high incidence of recurrence after curative resection, and is the fourth leading cause of cancer-related death in the United States (1). With the recent development of advanced multimodal pancreatic cancer treatments, the overall 5-year survival rate has risen to 8.8% (1). However, the majority of patients are inoperable at the time of diagnosis due to locally advanced or metastatic disease. Patients with metastatic disease have a one-year median survival (2). Surgical resection is the only option for cure, but less than 20% of cases diagnosed with pancreatic cancer are surgically resectable, while the remaining cases have involvement of major abdominal vessels and/or distant metastatic disease and are considered unresectable (3). There is no significant laboratory data studied so far in the evaluation of unresectability. Imaging studies are the most used method in determining unresectability. Multidetector computed tomography is the most widely used imaging modality for assessing local disease spread, vascular involvement, and distant metastases (CT). It has been reported that it predicts resectability 77% accurately and unresectability 93% accurately (4). However, the test has a low positive predictive value, and unresectable lesions develop at laparotomy in approximately 25-50% of patients who were thought to have resectable disease on computed tomography (5). It remains difficult to identify patients who would not benefit from surgical exploration by preoperative imaging (6). As a result, unnecessary laparotomy is applied to patients and this surgical intervention adds extra morbidity and mortality to the patient.

In this study, the predictive value of hematological parameters and CA19-9 were investigated in the evaluation of inoperability by comparing resectable and unresectable patients over the laboratory data of patients with pancreatic cancer.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 02.03.2022, Decision No: 15). With the ethics committee approval, the data were scanned retrospectively using the Hospital Information Management System.

The study examined 147 individuals with pancreatic cancer who were diagnosed at Hitit Univesity Erol Olçok Training and Research Hospital between March 15, 2015, and October 15, 2021. The study included patients over the age of 18 who had been diagnosed with pancreatic cancer. Patients under the age of 18, those with a disease that could affect their blood values (cirrhosis, chronic kidney failure), pregnant and lactating women, patients from a small population (those without mental faculties, soldiers, and convicts), and those whose data could not be obtained were all excluded from the study.

The demographic information of the patients, such as their age and gender, was recorded. The patients were divided into study groups as those who underwent surgery and were resectable (Group 1) and those who were evaluated both radiologically and intraoperatively as unresectable/inoperable (large vessel invasion, presence of metastatic disease) in the perioperative period (Group 2) (**Figure 1**). The clinical archive system was reviewed retrospectively, and patients whose data were fully accessible and who met the study criteria were included.

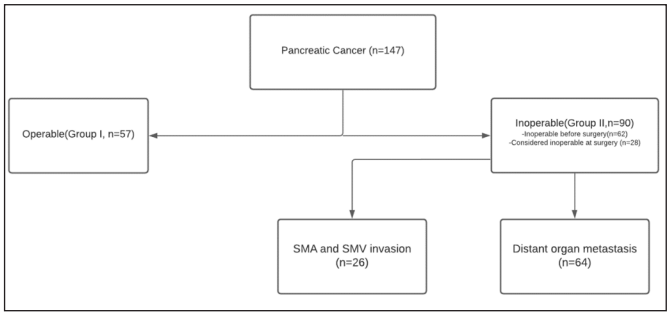

Figure 1. Flowchart of the operable group (Group I) and inoperable group (Group II).

The dimensions of the pancreatic tumor were measured from the triphasic computed tomography data of all patients in the preoperative period. Monocyte (MO), lymphocyte (LY), platelet (P), neutrophil (NE), mean platelet volume (MPV), platelet distribution width (PDW), C-reactive protein (CRP), and cancer antigen 19-9 (CA19-9) values were measured in laboratory samples collected during the patients' preoperative period. Platelet/mean platelet volume ratio (P/MPV), platelet/platelet distribution volume ratio (P/PDW), neutrophile/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and C- reactive protein/lymphocyte values were computed using the information collected.

Statistical Analysis

The SPSS program for Windows version 22.0 was used to assess the data analysis (SPSS Inc., Chicago, Illinois, USA). The mean + standard deviations are used to represent continuous variables having a normally distributed distribution. To demonstrate that the parameters followed a normal distribution, the Kolmogorov-Smirnov test was used. The diagnostic capacity of Laboratory index was evaluated using a receiver operating characteristic (ROC) curve analysis, and ROC curves were generated to analyse the balance between sensitivity and specificity. P value 0.05 was used to determine statistical significance.

RESULTS

The study included 147 patients who had been diagnosed with pancreatic cancer and were being followed up on. The mean age of the patients who took part in the study was determined to be 69.5 (11.3±SD). 47 (31.2%) of the patients included in the study were female and 100 of them (68.8%) were male. There were 57 patients in Group I and 90 patients in Group II. It was seen that 62 patients in Group 2 were considered inoperable as a result of the preoperative evaluations, and 28 patients were evaluated as operable in the preoperative examinations and underwent surgery but were considered unresectable during the operation.

Group I had a mean age of 69.1 (10.6 SD), while group II had a mean age of 69.8 (11.2 SD). There was no statistical difference between the two groups in terms of age and gender distribution (p:0.870, p:756, respectively). The age, gender, and test result characteristics of all patients are shown in **Table 1.**

Table 1. Characteristic of subjects in Group I and Group II

	Total (n=147) (SD)	Group I (n=57)	Group II (n=90)	p value
Age, years	69.8 (11.2)	68.9 (10.6)	69.8 (11.2)	0.870
Sex				0.756
Male	100 (68.8%)	30 (70.2%)	70 (77.7%)	
Female	47 (31.2%)	17 (29.8%)	30 (22.3%)	
NLR	5.4 (8.2)	3.4 (2.7)	6.7 (10.1)	0.001
Mass size,mm	34.4 (14.8)	27.9 (13.9)	38.5 (13.9)	0.001
LMR	3.02 (2.1)	3.1 (1.9)	2.9 (2.2)	0.262
P/PDW	19.4 (11.6)	(20.8 (11.1)	18.6 (11.9)	0.080
P/MPV	24.5 (11.9)	26.1 (11.2)	23.6 (12.2)	0.107
P/RDW	16.2 (7.2)	16.6 (5.6)	16.1 (8.1)	0.218
CRP/L	35.9 (139.4)	11.9 (13.1)	41.2 (176.6)	0.001
CRP	34.1 (50.4)	17.4 (19.2)	44.5 (60.4)	0.001
PDW	13.9 (2.7)	13.4 (2.5)	14.2 (2.8)	0.136
CA 19-9	3801 (15,904)	924 (2796.5)	5624 (20,034)	0.001

NLR:Neutrophil/lymphocyte ratio, LMR:Lymphocyte/monocyte ratio, P/PDW:Platelet/platelet distribution width ratio, P/MPV:Platelet/mean platalet volume ratio, P/RDW:Platelet/red blood cell distribution width, L: Lymphocyte CRP: C-reactive protein, Statistically significant data bolded

When the patients' NLR, mass size, CRP/L, CRP, and Ca-19.9 levels were compared between groups, a significant difference was observed (**Table 1**). According to this, it was determined that as NLR increased and the size of the mass was larger, the probability of patients being inoperable increased. Furthermore, increases in Ca-19.9, CRP, and CRP/L ratio were statistically significant in terms of patient inoperability. Platelet/platelet distribution width ratio (P/PDW) and Platelet/mean platelet volume ratio (P/MPV) values did not differ statistically between groups.

ROC analysis was used to investigate the predictive value of these statistically significant results.

As a result of the study, the tumor size with the highest AUC value was found. It had a sensitivity of 77.8 % and a specificity of 61.4 % at a cut-off value of 29 mm. CA 19-9 also had the second highest AUC value. When the predictive value of the NLR value obtained from the routine laboratory values in separating the groups is examined, it was seen that AUC value was 0.679. Its sensitivity was 64.4% and specificity was 63.2 % in differentiating inoperable patients at a cut-off value of 3.21. (**Table 2**) (**Figure 2**).

Table 2. Sensitivity, specificity and area under the curve of NLR, mass size, CRP/L,CRP and CA 19-9

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
NLR	0.679	3.21	64.4	63.2
Mass size, mm	0.742	29	77.8	61.4
CRP/L	0.683	10.6	62.2	61.4
CRP	0.674	14.1	61.1	63.2
CA 19-9	0.705	14.5	63.3	63.2

NLR:Neutrophil/lymphocyte ratio, L: Lymphocyte, CRP: C-reactive protein

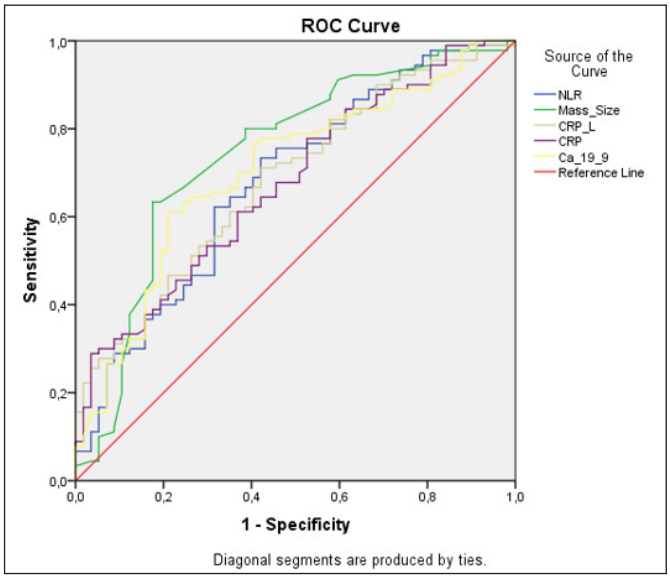

Figure 2. ROC curves for subjects (Group I vs Group II)

When the age, NLR, mass size, P/PDW, P/MPV, CRP, CRP/L, PDW, and CA 19-9 values of patients in Group 2 with SMA and SMV invasion (n:26) were compared to those in Group I, a statistical difference was discovered between age, NLR, mass size, P/PDW, P/MPV, CRP, CRP/L, PDW, and CA 19-9 values were compared. In the ROC analysis, the highest AUC value belonged to mass size. At a cut-off value of 31.1 mm, it had 76.9 % sensitivity and 75.4 % specificity. Following that, at a cut-off value of 3.2, the NLR had 65.4 % sensitivity and 64.9 % specificity. In addition, the CA 19-9 value had a cut-off value of 158.8 with a sensitivity of 69.2% and a specificity of 68.4% (**Table 3**) (**Figure 3**).

Table 3. Sensitivity, specificity and area under the curve of NLR, mass size, CRP/L,CRP ,CA 19-9, P/PDW, P/MPV, PDW and age for SMA/SMV invasion

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
NLR	0.733	3.2	65.4	64.9
Mass size, mm	0.765	31.1	76.9	75.4
CRP/L	0.686	10.3	61.5	59.6
CRP	0.662	14.1	61.5	61.4
Ca-19-9	0.672	158.8	69.2	68.4
P/PDW	0.362	17.1	46.2	43.9
P/MPV	0.365	21.2	42.3	40.4
PDW	0.641	57.7	57.9	57.9
Age,years	0.650	72.4	57.7	57.9

NLR: Neutrophil/lymphocyte ratio, L: Lymphocyte, CRP: C-reactive protein, P/PDW: Platelet/platelet distribution width ratio, P/MPV:Platelet/mean platelet volume ratio

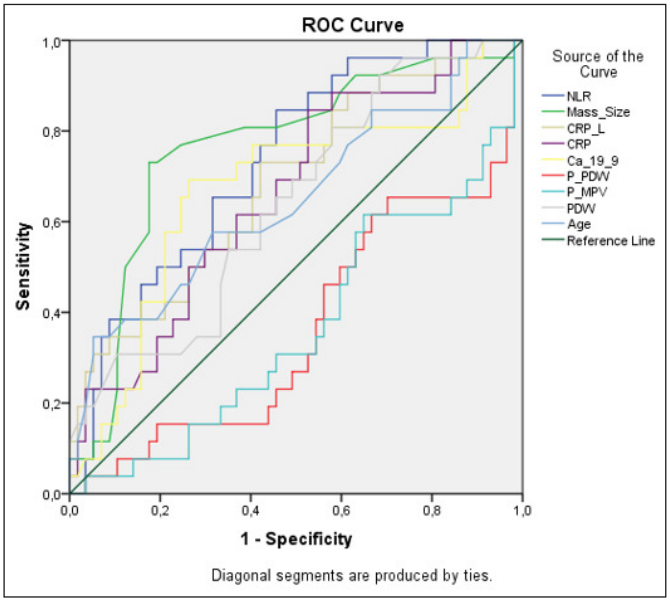

Figure 3. ROC curves for subjects (Group I vs Group II)

DISCUSSION

As a result, pancreatic cancer is the deadliest cancer. Even though surgery is still the primary treatment, most patients have missed out on this opportunity at the time of application. In our study, NLR, CRP, CRP/L, CA 19-9 levels, and tumour mass were found to be extremely important in terms of the possibility of resectable surgery. These values, we believe, can help us avoid unnecessary laparotomies in cases of unresectability or vascular invasion.

Pancreatic cancers are among the types of cancers which have an extremely poor prognosis and a high mortality rate. Late discoveries lead to late diagnosis, resulting in the disease being clinically detected at advanced stages. Pancreatic cancers are cancers with a high risk of vascular invasion due to their anatomical structure. Therefore, the possibility of inoperability is high. Imaging techniques, in particular, are utilized to assess the operability of pancreatic cancer. According to the NCCN guideline, superior mesenteric artery (SMA), celiac artery involvement, unresectable superior mesenteric vein (SMV), portal vein involvement, and distant organ metastases are considered locally advanced pancreatic cancer in imaging methods (7). Locally advanced pancreatic cancer has no place for surgical treatment and adjuvant chemotherapy is planned (8). However, imaging methods reduce the sensitivity to 77%, especially in lesions less than 2 cm (9). As a result, unnecessary laparotomy is performed.

Pancreatic cancer is more common in men than in women. Men are 30% more likely than women to develop pancreatic cancer, according to Shaib's research (10). Pancreatic cancer was found to be 37.6 % more common in men in this study, which was thought to be consistent with previous research.

The increase in mass size in pancreatic cancers adversely affects the risk of vascular involvement and prognosis. According to Phoa et al.'s (11) research, lesions larger than 3 cm increase unresectability and worsen prognosis. According to Chatelain et al. (12), tumours larger than 2 cm in diameter have a poor prognosis. Takahashi et al. (13) discovered that lesions larger than 2 cm in diameter reduced the likelihood of R0 resection. According to our research, the mass size in terms of unresectability had a sensitivity of 77.8 % and a specificity of 61.4 % at a cut-off value of 29 mm. Furthermore, at a cut-off value of 31.1 mm, the mass size demonstrated 76.9 % sensitivity and 75.4 % specificity in terms of large vessel invasion. These findings were determined to be statistically significant and compatible with the literature data.

A high neutrophil count in the blood is frequently the cause of high NLR, which is accompanied by lymphocytopenia. A high neutrophil count may help to form and progress a neoplasia by creating a favourable tumour microenvironment in which many growth factors are released (14). Various studies have demonstrated that NLR predicts the course of disease in many cancer types, including oesophageal, stomach, colorectal, bladder, lung, breast, hepatocellular carcinoma, and pancreas cancer (15). In a study of patients with locally advanced and metastatic pancreatic cancer, Teo et al. (16) found that patients with a high baseline NLR had a shorter survival time. In their study, Stotz et al. (17) revealed that NLR increased in inoperable patients. NLR values between 2.5 and 5 have been linked to metastatic pancreatic cancer and a poor prognosis in various studies. The cut-off value for NLR in our study was 3.21, and it was discovered that the probability of locally progressed and metastatic pancreatic cancer rose over this value, which is consistent with the literature. Moreover, the risk for NLR was found to be elevated at a cut-off value of 3.2 in the vascular invasion evaluation, which was not stated separately in

previous research, and we believe that these findings will contribute to the literature.

Wiese's study (18) found that patients with elevated CRP levels in pancreatic cancer had a considerably lower overall survival. C-reactive protein/lymphocyte ratios greater than 1.8 have recently been linked to poor survival. A ratio greater than 1.8 was also identified as an independent risk factor for death in pancreatic cancer stages II, III, and IV (19). Correspondingly, an increase in CRP before surgery has been linked to invasion and a poor prognosis in pancreatic cancers (20). Similarly, preoperatively evaluated CRP increase has been linked to invasion and poor prognosis in pancreatic cancers (20). Likewise, when the patients were divided into groups based on vascular invasion, it was discovered that those with a high preoperative CRP and CRP/L ratio had more SMA and SMV invasions.

CA 19-9 is the most commonly used serum biomarker for detecting pancreatic cancer. According to Young Choon Kim's (21) research, the possibility of resectability decreased once the cut-off value for CA 19-9 was reached at 92.77. In another study, a cut-off value of 130U/ml was determined for Ca19-9, and it was observed that the probability of unresectability was high above this value (22). In our study, CA 19-9 elevation was observed to be increased in inoperable pancreatic cancers. These studies' findings support the link between tumour stage and CA19-9 level. However, this study emphasizes the relationship between vascular invasion and CA19-9, which has not been mentioned before. As a result, pancreatic cancer with a CA 19-9 cut-off value of 158.8 U/ml was discovered to have a high risk of SMA and SMV invasion.

Although the findings of this study are consistent with previous research, the fact that it is a single-centre study may be a disadvantage. Besides that, the significantly higher proportion of inoperable patients versus operable patients suggests that the patient group may have delayed hospital admission due to their low socioeconomic status. Furthermore, the recent increase in the number of inoperable patients shows that late admission may be linked to the COVID-19 epidemic, which has been going on for nearly two years.

CONCLUSION

The high NLR, CRP, CRP/L, CA 19-9 values in our study enabled us to conclude that they are predictive markers for inoperable pancreatic cancer. In addition, the probability of locally advanced and metastatic pancreatic cancer was found to exceed this value. These values, we believe, can help us avoid unnecessary laparotomies in cases of unresectability or vascular invasion.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 02.03.2022, Decision No: 15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict Of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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